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Application of: THOMSEN et al.

Group Art Unit: To be assigned

Application No.: 10/009,945

Examiner: To be assigned

Filed: December 11, 2001

Attorney Docket No.: 10624-092-999

For: ANTAGONISTS OF BMP AND TGFB  
SIGNALING PATHWAYS

**INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)(3)**

**BOX APPLICATIONS**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Pursuant to Applicants' duty of disclosure under 37 C.F.R. § 1.56, enclosed is a copy of ninety publications (References AA and DL).

Applicants submit herewith "List of References Cited." Identification of the listed references is not to be construed as an admission of Applicant or Attorneys for Applicant that such references are available as "prior art" against the subject application.

Applicants respectfully request that this information disclosure statement be considered by the Examiner and made of record in the above-identified application by the Examiner's completion and return of the revised Form PTO.

Applicants believe no fee is due with the submission of this information disclosure statement. If a fee is due, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

A copy of this correspondence is enclosed.

Respectfully submitted,

by Jacqueline Benn  
Reg. No. 43,496

Date: January 10, 2003

Anthony M. Insogna 35,203  
Anthony M. Insogna (Reg No.)

**PENNIE & EDMONDS LLP**  
1155 Avenue of the Americas  
New York, New York 10036  
Tel. No. (212) 790-9090

Enclosures



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<b>LIST OF REFERENCES CITED BY APPLICANT</b> <i>(Use several sheets if necessary)</i>		ATTY. DOCKET NO.	APPLICATION NO.
		10624-0092-999	10/009,945
		APPLICANT	
		Thomsen, G. and Wrana, J.	

U.S. PATENT DOCUMENTS							
*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	6,103,869	08/15/2000	Souchelnytokyi et al.	530	330	
	AB	6,087,122	07/11/2000	Hustad et al.	435	29	
	AC	6,060,262	05/09/2000	Beer-Romero et al.	435	15	
	AD	6,001,619	12/14/1999	Beach et al.	435	193	
	AE	09/385,198	08/30/1999	Hoekstra et al.			

FOREIGN PATENT DOCUMENTS							
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION
							YES NO

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)	
AF	Afrakhte, et al. 1998. "Induction of Inhibitory Smad6 and Smad7 mRNA by TGF- $\beta$ family members," Biochemical and Biophysical Research Communications 244: 505-511.
AG	Baker, et al. 1996. "A novel mesoderm inducer, Madr2, functions in the activin signal transduction pathway," Genes & Development 10:1880-1889.
AH	Bartel, et al. 1990. "The recognition component of the N-end rule pathway," EMBO Journal 9: 3179-3189.
AI	Bartel, et al. 1995. "Analyzing protein-protein interactions using two-hybrid system," Methods in Enzymology, Vol. 254, (24):1-263.
AJ	Bashirullah, et al. 1998. "RNA Localization in Development," Annu. Rev. Biochem. 67:335-94.
AK	Bitzer, et al. 2000. "A mechanism of suppression of TGF- $\beta$ /Smad signaling by NF- $\kappa$ B/Rel A," Genes & Development 14:187-197.
AL	Bonifacino, et al. 1998. "Ubiquitin and the Control of Protein Fate in the Secretory and Endocytic Pathways," Ann. Rev. Cell. Biol. 14:19-57.
AM	Chen, et al. 1995. "The WW domain of Yes-associated protein binds a proline-rich ligand that differs from the consensus established for Src homology 3-binding modules," Poc. Natl. Acad. Sci. USA 82:7819-7823.
AN	Chung, et al. 1998. "A novel, putative MEK kinase controls developmental timing and spatial patterning in Dictyostelium and is regulated by ubiquitin-mediated protein degradation," Genes Dev. 12: 3564-78.
AO	Coffman, T.M., 1997. "A genetic approach for studying the physiology of the Type 1A (AT <sub>1A</sub> ) Angiotensin Receptor," Seminars in Nephrology 17:404-411.
AP	Deryck, et al., 1998, "Smads: Transcriptional Activators of TGF- $\beta$ Responses," Cell 19:737-740.
AQ	Dickson, B.J., 1998. "Photoreceptor development: Breaking down the barriers," Current Biology 8:R90-R92.
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AS	Epps, et al. 1998. "The <i>Drosophila semushi</i> mutation blocks nuclear import of Bicoid during embryogenesis," <i>Current Biology</i> 8:1277-1280.
AT	Esther, Jr., et al. 1996. "Mice Lacking Angiotensin-Converting Enzyme Have Low Blood Pressure, Renal Pathology, and Reduced Male Fertility," <i>Laboratory Investigation</i> 74:953.
AU	Fainsod, et al. 1994. "On the function of BMP-4 in patterning the marginal zone of the <i>Xenopus</i> embryo," <i>Embo J</i> 13:5015-25.
AV	Gilboa, et al. 1998. "Oligomeric structure of Type I and Type II transforming growth Factor $\beta$ Receptors: homodimers form in the ER and persist at the Plasma Membrane," <i>J. Cell Biol.</i> 140:767-777.
AW	Govers, et al. 1999. "Identification of a novel ubiquitin conjugation motif, required for ligand-induced internalization of the growth hormone receptor," <i>EMBO J.</i> 18:28-36.
AX	Graff, et al. 1996. "Xenopus Mad proteins transduce distinct subsets of signals for the TGF $\beta$ Superfamily," <i>Cell</i> 86:1-20.
AY	Harland, et al. 1997. "Formation and function of Spemann's Organizer," <i>Ann. Rev. Cell Biol.</i> 13:611-667.
AZ	Harvey, et al. 1999. "Nedd4-like proteins: an emerging family of ubiquitin-protein ligases implicated in diverse cellular functions," <i>Trends Cell Biol.</i> 9:166-169.
BA	Hayashi, et al. 1997. "The MAD-Related protein Smad7 Associates with the TGF $\beta$ Receptor and Functions as an antagonist of TGF $\beta$ signaling," <i>Cell</i> 89:1165-1173.
BB	Hein, et al. 1995. "NPI1, an essential yeast gene involved in induced degradation of Gap1 and Fur4 permeases, encodes the RspS ubiquitin-protein ligase," <i>Mol. Microbiol.</i> 18:77-87.
BC	Heldin, et al. 1997. "TGF- $\beta$ signalling from cell membrane to nucleus through SMAD proteins," <i>Nature</i> 390:465-71.
BD	Hemmati-Brivanlou, et al. 1995. "Ventral mesodermal patterning in <i>Xenopus</i> Embryos: expression patterns and activities of BMP-2 and BMP-4," <i>Dev. Genet.</i> 17:78-89.
BE	Hemmati-Brivanlou, et al. 1997. "Vertebrate Embryonic Cells will become nerve cells unless told otherwise," <i>Cell</i> 88:13-17.
BF	Henis, et al. 1994. "The Types II and III transforming growth Factor- $\beta$ Receptors form Homo-Oligomers," <i>J. Cell Biol.</i> 126:139-154.
BG	Hershko, et al. 1998. "The Ubiquitin System," <i>Ann. Rev. Biochem.</i> 67:425-479.
BH	Hicke, L., 1999. "Gettin' down with ubiquitin: turning off cell-surface receptors, transporters and channels," <i>Trends Cell Biol.</i> 9:107-112.
BI	Hochstrasser, M., 1996. "Ubiquitin-Dependent protein degradation," <i>Ann. Rev. Genet.</i> 30:405-439.
BJ	Hoodless, et al. 1996. "MADR1, a MAD-Related protein that functions in BMP2 signaling pathways", <i>Cell</i> 85:489-500.
BK	Horb, et al. 1997. "A vegetally-localized T-box transcription factor in <i>Xenopus</i> eggs specifies mesoderm and endoderm and is essential for embryonic mesoderm formation," <i>Dev.</i> 124:1689-1698.
BL	Huang, et al. 1995. "Control of cell fate by a deubiquitinating enzyme encoded by the fat facets gene," <i>Science</i> 270:1828-31.
BM	Huibregtse, et al. 1995. "A family of proteins structurally and functionally related to the E6-AP ubiquitin-protein ligase," <i>Proc. Natl. Acad. Sci. U.S.A.</i> 92:2563-7.

	BN	Imamura, et al. 1997. "Smad6 inhibits signaling by the TGF- $\beta$ superfamily," <i>Nature</i> 389:622-626.
	BO	Ishisaki, et al. 1998. "Smad7 is an activin-inducible inhibitor of activin-induced growth arrest and apoptosis in Mouse B Cells," <i>J. Biol. Chem.</i> 273:24293-24296.
	BP	Itoh, et al. 1998. "Transforming growth factor $\beta$ 1 induces nuclear export of inhibitory Smad7," <i>J. Biol. Chem.</i> 273:29195-29201.
	BQ	Jiang, et al. 1998. "Regulation of the Hedgehog and Wingless signalling pathways by the F-box/WD40-repeat protein Slimb," <i>Nature</i> 391:493-6.
	BR	Joazeiro, et al. 1999. "The tyrosine kinase negative regulator c-Cbl as a RING-Type, E2-Dependent ubiquitin-protein ligase," <i>Science</i> 286:309-312.
	BS	Jonk, et al. 1998. "Identification and functional characterization of a Smad binding element (SBE) in the JunB promoter that acts as a transforming growth Factor- $\beta$ , activin, and bone morphogenetic protein-inducible enhancer," <i>J. Biol. Chem.</i> 273:21145.
	BT	Joseph, et al. 1998. "Mutant Vg1 ligands disrupt endoderm and mesoderm formation in <i>Xenopus</i> embryos," <i>Development</i> 125:2677-85.
	BU	Kawabata, et al. 1998. "Signal transduction by bone morphogenetic proteins," <i>Cytokine Growth Factor Rev.</i> 9:49-61.
	BV	Kimelman, et al. 1998. "Mesoderm Induction: A Postmodern View," <i>Cell</i> 94:419-21.
	BW	Kim, et al. 1997, "Drosophila Mad binds to DNA and directly mediates activation of vestigial by Decapentaplegic," <i>Nature</i> 388:304.
	BX	Kretzschmar, et al. 1997. "The TGF- $\beta$ family mediator Smad1 is phosphorylated directly and activated functionally by the BMP receptor kinase," <i>Genes Dev.</i> 11:984-95.
	BY	Kumar, et al. 1997. "cDNA Cloning, expression analysis, and mapping of the Mouse Nedd4 Gene," <i>Genomics</i> 40:435-43.
	BZ	Kwon, et al. 1998. "The mouse and human genes encoding the recognition component of the N-end rule pathway," <i>Proc. Natl. Acad. Sci. U.S.A.</i> 95:7898-903.
	CA	Levkowitz, et al. 1999. "Ubiquitin ligase activity and tyrosine phosphorylation underlie suppression of growth factor signaling by c-Cbl/Sli-1," <i>Mol. Cell</i> 4:1029-1040.
	CB	Lindsay, et al. 1998. "A deubiquitinating enzyme that disassembles free polyubiquitin chains is required for development but not growth in <i>dictyostelium</i> ," <i>J. Bio. Chem.</i> 273:24131-8.
	CC	Macias-Silva, et al. 1996. "MADR2 is a substrate of the TGF $\beta$ receptor and its phosphorylation is required for nuclear accumulation and signaling," <i>Cell</i> 87:1215-1224.
	CD	Macias-Silva, et al. 1998. "Specific activation of Smad1 signaling pathways by the BMP7 Type 1 Receptor, ALK2," <i>J. Biol. Chem.</i> 273:25628-36.
	CE	Massague, et al. 2000. "Controlling TGF- $\beta$ signaling," <i>Genes Deve.</i> 14:627-644.
	CF	Massague, J., 1998. "TGF- $\beta$ signal transduction," <i>Ann. Rev. Biochem.</i> 67:753-791.
	CG	Miyazono, K., 2000. "TGF- $\beta$ signaling by Smad proteins," <i>Cyto. Growth Factor Rev.</i> 11:15-22.
	CH	Murakami, et al. 1996. "Hypertensive and Hypotensive Mice produced by the introduction and disruption of genes on the Renin-Angiotensin system," <i>Blood Press. Suppl.</i> 2:36.

	CI	Muralidhar, et al. 1993. "The <i>Drosophila</i> bendless gene encodes a neural protein related to ubiquitin-conjugating enzymes," <i>Neuron</i> 11:253-66.
	CJ	Nakao, et al. 1997. "Identification of Smad7, a TGF $\beta$ -inducible antagonist of TGF- $\beta$ signalling," <i>Nature</i> 389:631-635.
	CK	Nalefski, et al. 1996. "The C2 domain calcium-binding motif: Structural and functional diversity," <i>Protein Sci.</i> 5:2375-2390.
	CL	Nefsky, et al. 1996. "Pub1 acts as an E6-AP-like protein ubiquitin ligase in the degradation of cdc25," <i>Embo. J.</i> 15:1301-1312.
	CM	Patton, et al. 1998. "Combinatorial control in ubiquitin-dependent proteolysis: don't Skp the F-box hypothesis," <i>Trends. Genet.</i> 14:236-243.
	CN	Plant, et al. 1997. "The c2 domain of the ubiquitin protein ligase Nedd4 mediates Ca $^{2+}$ -dependent plasma membrane localization," <i>J. Biol. Chem.</i> 272:32329-36.
	CO	Pukatzki, et al. 1998. "A novel component involved in ubiquitination is required for development of <i>Dictyostelium discoideum</i> ," <i>J Biol. Chem.</i> 273:24131-8.
	CP	Reddi, A. H., 1998. "Role of morphogenetic proteins in skeletal tissue engineering and regeneration," <i>Nature Biotech.</i> 16:247-252.
	CQ	Reeck, et al. 1987. "Homology" in proteins and nucleic acids: A terminology muddle and a way out of it," <i>Cell</i> 50:667.
	CR	Rotin, D., 1998. "WW (WWP) domains: From structure to function," <i>Curr. Topics Microbiol. Immunol.</i> 228:115-133.
	CS	Sasai, et al. 1997. "Ectodermal patterning in vertebrate embryos," <i>Dev. Biol.</i> 182:5-20.
	CT	Scheiffner, et al. 1993. "The HPV-16 E6 and E6-AP Complex functions as a ubiquitin-protein ligase in the ubiquitination of p53," <i>Cell</i> 75:495-505.
	CU	Staub, et al. 1997. "Immunolocalization of the ubiquitin-protein ligase Nedd4 in tissues expressing the epithelial Na $^{+}$ channel (EnaC)," <i>Am. J Physiol.</i> 272:C1871-80.
	CV	Staub, et al. 2000. "Regulation of stability and function of the epithelial Na $^{+}$ channel (EnaC) by ubiquitination," <i>Kidney Int.</i> 57:809-815
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	CX	Staub, et al. 1996. "WW domains," <i>Structure</i> 4:495-499.
	CY	Staub, et al. 1996. "WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na $^{+}$ channel deleted in Liddle's syndrome," <i>EMBO J.</i> 15:2371-2380.
	CZ	Suzuki, et al. 1997. "Smad5 induces ventral fates in <i>Xenopus</i> embryo," <i>Dev. Biol.</i> 184:402-405.
	DA	Takase, et al. 1998. "Induction of Smad6 mRNA by bone morphogenetic proteins," <i>Biochem. Biophys. Res. Commun.</i> 244:26-29.
	DB	Thomsen, G.H., 1997. "Antagonism within and around the organizer: BMP inhibitors in vertebrate body patterning," <i>Trends Genet.</i> 13:209-211.
	DC	Thomsen, G.H., 1996. "Xenopus mothers against decapentaplegic is an embryonic ventralizing agent that acts downstream of the BMP-2/4 receptor," <i>Development</i> 122:2359-66.

	DD	Tsukazaki, et al. 1998. "SARA , a FYVE domain protein that recruits Smad2 to the TGF $\beta$ receptor," Cell 95:799-791.
	DE	Ulloa, et al. 1999. "Inhibition of transforming growth factor- $\beta$ /SMAD signalling by the interferon- $\gamma$ /STAT pathway," Nature 397:710-713.
	DF	van Kerkhof, et al. 2000. "Endocytosis and degradation of the growth hormone receptor are proteasome-dependent," J. Biol. Chem. 275:1575-1580.
	DG	Wang, , et al. 1999. "Functional domains of the Rsp5 Ubiquitin-protein ligase," Mol. Cell Biol. 19:342-52.
	DH	Whitman, M., 1998. "Smads and early developmental signaling by the TGF $\beta$ superfamily," Genes and Dev. 12:2445-2462.
	DI	Wigler, et al. 1979. "Transformation of mammalian cells with genes from prokaryotes and eukaryotes," Cell 16:777-785.
	DJ	Wilson, et al. 1997. "Concentration-dependent patterning of the Xenopus ectoderm by BMP4 and its signal transducer Smad1," Dev. 124:3177-3184.
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	DL	Wrana, et al. 2000. "The Smad pathway," Cytokine & Growth Factor Reviews 11:5-13.
EXAMINER		DATE CONSIDERED

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